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10/568,761	02/21/2006	Takamasa Watanabe	Q116808	6669

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/01/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/568,761	WATANABE ET AL.	
	Examiner	Art Unit	
	MAHER HADDAD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,20 and 31-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/16/2011 has been entered.

2. Claims 19-20 and 31-37 are pending and under examination as they read on a method for improving or treating inflammatory bowel disease (IBD) comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody to a patient in need thereof.

Claims 19, 20, 31, 32 and 35-37 are Patentable Under 35 U.S.C. § 102(b)

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 19-20, 32 and 35-37 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S Pat. No. 6,423,501 OR WO/ 98/25647 for the same reasons set forth in the previous Office Actions.

5. Claims 19-20, 31-32 and 35-37 stand rejected under 35 U.S.C. 102(b) as being anticipated by Curd et al (WO 00/67796) for the same reasons set forth in the previous Office Actions.

Applicant's arguments, filed 03/16/2011, have been fully considered, but have not been found convincing.

Applicants disagree with the Office's logic as to why (a) the rejection does not constitute impermissible picking and choosing, and (b) why the laundry lists of Fleming et al. and Curd et al. - when relied upon in conjunction as the Office has done - do not constitute a generic disclosure. For the reasons set forth below, the rejections are sustained on flawed logic, are inconsistent with relevant law, and must therefore be withdrawn.

First, turning to the Office's reasoning as to why the selection of the different claim elements from Fleming et al. and Curd et al. does not constitute impermissible picking-and- choosing, the Office attempts to justify the rejection by arguing that the items listed within a given laundry list are directly related to each other. For example, the Office argues that "all the diseases" recited in Fleming et al. and Curd et al. are "directly related" as being autoimmune diseases, and that "all

the antagonists" of Curd et al. are "directly related" as being B-cell markers. This argument, however, is predicated on a misunderstanding of the law. The relevant "direct" relationship in the instant case is not that asserted in the rejection. To the contrary, *Arkley* makes clear that the "direct relationship" must be between the specific claim elements themselves. Accordingly, in the instant case, the direct relationship must be between those elements selected from different laundry lists (i. e., CD81, inflammatory bowel disease, and an antibody), not merely between the alternatives recited within each laundry list.

Indeed, under the logic set forth in the rejection, it would appear that even in those instances where the courts have found no anticipation of a chemical species by a generic chemical formula, because picking-and-choosing of specific substituents for several different moieties was necessary, see *In re Arkley*, anticipation would have been proper. By way of example, all the possible substituents disclosed for a given position on a chemical formula could be argued to be "directly related" to each other by the teachings of the cited reference because they are all disclosed as being suitable for use at this position.

As noted above, the relevant relationship, as expressly articulated in *Arkley*, is whether there exists a direct relationship linking together all the elements claimed. Applicants reiterate that the cited references disclose no such direct relationship. That inflammatory bowel disease, for example, is related to the other diseases listed in the cited references (because they are all inflammatory diseases), is irrelevant to prove that the cited references disclose a direct relationship between CD81, inflammatory bowel disease, and an antibody. Because the rejection is sustained on a proposition not supported by law, the rejection must be withdrawn.

Second, Applicants disagree with the Office's conclusion that the relied- upon portions of Curd et al. and Fleming et al. do not constitute generic disclosures. Analogous to a generic chemical formula that recites several variable positions at which a myriad of substituents are listed as being suitable, see *Arkley*, Fleming et al. (and to a greater extent Curd et al.) generically discloses treatment of a disease with an agent, and provides a laundry list of both agents and diseases that can be selected in such a generic method. In the case of Curd et al., this is further compounded by the fact that CD81 must also be selected from a laundry list of different B-cell markers.

However, as Applicants have already noted on the record,(pages 7-10 of the amendement filed 10/6/2010), the combination of CD81, antibody, and inflammatory bowel disease claimed by Applicants is a species that must be selected from the generic disclosures of Curd et al. and Fleming et al. Because this *species* is not disclosed either expressly or inherently by either reference, to hold that it is described for purposes of anticipation requires the creation, *ex post facto*, of this species by picking and choosing from the laundry lists of Curd et al. and Fleming et al. - which when taken together constitute a genus of possible treatment methods. Applicants maintain that the generic disclosures of Curd et al. and Fleming et al. are sufficiently broad, and the species of methods encompassed therein sufficiently diverse, that they do not disclose the claimed combination with "sufficient specificity," as is required for a genus to anticipate a species. See *In re Ruschig*, 343 F.2d 965,974-75 (C.C.P.A. 1965).

In maintaining the rejection, the Office asserts that because CD81, inflammatory bowel disease, and an antibody are each explicitly named in Fleming et al. and Curd et al., despite being located in different laundry lists of alternatives, anticipation is proper because when "the [claimed] species is clearly named, the species claim is anticipated no matter how many other species are additionally named," citing M.P.E.P. § 2131.02 and *Ex parte A*. However, Applicants respectfully submit that this assertion is also predicated on a misunderstanding of the law. As acknowledged by the Office, M.P.E.P. § 2131.02 and *Ex parte A* pertain to the situation where the species itself is explicitly named. As noted above, the relevant species in the instant case is the combination of CD81, antibody, and inflammatory bowel disease - and this specific combination is not explicitly named, or inherently disclosed, anywhere in Fleming et al. and Curd et al. To the contrary, it can only be obtained by picking and choosing from the laundry list disclosures therein. This clearly is not a species that is "clearly named," under M.P.E.P. § 2131.02 and *Ex parte A*; such would require an express and specific disclosure of using an anti-CD81 antibody to treat inflammatory bowel disease, without any selection from any alternatives being required. Clearly this is not the case with either Fleming et al. and Curd et al.

However, it remains the Examiner's position that the prior art of Fleming et al patent explicitly discloses the specific disease name (i.e., IBD) and the specific agent (anti-CD81 antibodies) of the claimed method. Again, it is immediately apparent that the facts in this case do not involve any "need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference." All the 20 diseases listed by Fleming et al patent are linked by CD81 and the inhibition of inflammatory responses associated with these disorders. Moreover, 20 disorders are very small genus of diseases and the claimed inflammatory bowel disease is taught in the Fleming et al disclosure. In addition, the three agents are directly related to each other in that they all induce CD81-mediated signaling transduction. The three agents are small recognizable class of compounds with common properties. All that is needed to implement the disclosure of Fleming et al is to treat the inflammatory responses of IBD with anti-CD81 antibody which induces CD81-mediated signal transduction. The three agents describe in the prior art of Fleming et al are limited class which are adequately described as induces CD81-mediated signal transduction. Fleming et al discloses that in particular embodiments the antibody is 5D1 or IA12 (see col., 9, II. 65 to col., 10, II. 3 in particular). That is the generic disclosure in the reference identified "specific preferences," which were met by the later-described species. Similarly, the diseases are also linked by inflammatory responses such as inflammatory bowel disease (i.e., Crohn's disease and ulcertive colitis) (see col., 13, lines 34-45).

The Examiner directs Applicant's attention to the MPEP at 2131.02 which states that "a genus does not always anticipate a claim to a species within the genus, however, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was

specifically taught. The Board compared the facts to the situation in which the compound was found in the *Merck Index*, saying that "the tenth edition of the *Merck Index* lists ten thousand compounds. In our view, each and every one of those compounds is 'described' as that term is used in 35 U.S.C. § 102(a), in that publication."). *Id.* at 1718".

With respect to Curd et al, Curd lists antagonists binding to a particular cell type, B-cell markers and autoimmune diseases, including the specific anti-CD81 antibody and IBD in claims 2 and 6. All the antagonists taught by Curd et al are directly related by being antagonist to B-cell markers and all the diseases are also directly related by being autoimmune disease. While all experiments in Curd et al are relate to the anti-CD20 antibody rituximab and no experimental detail is provided on the production and use of anti-CD81 antibodies, however, anti-CD81 antibodies and their use in treating autoimmune diseases including IBD are present in the claims of Curd et al. There is no reason that the ordinary artisan would need to pick and combined unrelated antagonist and diseases, as all that is required by the claims is a administering an anti-CD81 antibody to improve or treat inflammatory bowel disease (IBD). Applicant does not dispute that these antagonists and diseases are related by the B-cell markers and autoimmune diseases. The antagonist genus of Curd et al is linked by binding to the surface of B-cell markers and the diseases being autoimmune diseases. As in *Schaumann*, the Curd et al disclosed antagonists which bind to a B cell surface marker, and a disease that being autoimmune disease that each differed only by a single variable, such that only a limited number of antagonists/diseases was encompassed by the implied class.

Applicant submits that in addition to Fleming et al. and Curd et al. failing to describe the presently claimed invention with sufficient specificity for purposes of anticipation, as a corollary, neither reference enables the presently claimed method. As Applicants have previously pointed out, prior art containing broad disclosures of alternatives is non-enabling, and thus not anticipatory, where undue experimentation would be required to determine which combinations of alternatives are operable. See, e.g., *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.,* 545 F.3d 1312 (Fed. Cir. 2008). In *Impax*, the district court acknowledged that the allegedly anticipating disclosure contemplated that the compounds of the invention "are associated with the treatment of at least 8 different diseases." However, the court held that there "was nothing in the [disclosure] which would lead one to recognize that any specific compound, let alone riluzole, would be used to treat any specific disease." The court concluded that it would require undue experimentation to determine what compounds of the invention can be sued to treat each disease listed. The Federal Circuit affirmed the district court's reasoning, stating that it would have required "extensive experimentation to link riluzole with the treatment of ALS [the subject matter of the claim at issue].

However, the standard for what constitutes sufficient enablement of prior art reference for purpose of anticipation under 35 U.S.C. 102(b) differs from enablement standard under Section 112, in that the prior art reference need not demonstrate utility in order to serve as anticipating reference under Section 102. Here, Fleming et al. and Curd et al. are enabling in the sense that

each describes the claimed invention sufficiently to enable a person of ordinary skill in the are to carry out the claimed method for improving or treating inflammatory bowel disease comprising administering a therapeutic agent comprising an effective amount of anti-CD81 antibody to a patient in need thereof. Essentially, applicants are applying a higher standard of enablement to the anticipatory reference than is warranted. *See Rasmusson* at 1325 ("The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. In *In re Hafner*, 56 C.C.P.A. 1424, 410 F.2d 1403 (Cust. & Pat.App. 1969), the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim." Id. at 1405; *see Schoenwald*, 964 F.2d at 1124; *In re Samour*, 571 F.2d 559, 563- 64 (Cust. & Pat.App. 1978).") In the instant case, Applicant fails to provide any persuasive evidence that the `501 patent or `647 publication did not enable the instant claims. Applicant fails to provide evidence to overcome the presumption of enablement of the prior art as has done in the *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.,* 545 F.3d 1312 (Fed. Cir. 2008).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 31 and 33-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S Pat. No. 6,423,501 or WO 98/25647 or WO 00/67796, as applied to claims 19-20, 31-32 and 35-37, above, and further in view of and Owens et al (1994) for the same reasons set forth in the previous Office Actions.

Applicant's arguments, filed 03/16/2011, have been fully considered, but have not been found convincing.

Applicants note that Owens et al. is directed to the production of variant antibody molecules, such as Fab, F(ab')2, Fv or scFv molecules. As such, Owens et al. does nothing to rectify the

deficiencies of Fleming et al. and Curd et al., discussed above. Accordingly, those of ordinary skill in the art would not have arrived at the presently claimed invention for the same reasons as presented above, notwithstanding the disclosure of Owens et al.

It remains the Examiner's position that it is the Examiner's position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the anti–CD81 antibody taught by 6,423,501 or WO 98/25647 to Fab or F(ab')2 fragments taught by Owens et al. because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

Claims 19, 20 and 31-37 are Patentable Under 35 U.S.C. § 103(a)

8. Claims 19, 20 and 31-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US. Patent 6,423,501 OR WO 98/25647, as is evidenced by He (World J Gastroenterol 2004;10(3):309-318).

Given the shared disclosure of the WO/ 98/25647 publication and US Pat. No. 6,423,501, this rejection is made using the teachings of the US. Pat. No. 6,423,501.

The `501 patent teaches a method of improving and treating inflammatory condition in a mammal such as human (patient) comprising administering to the mammal an effective amount of an agent which induces CD81-mediated signal transduction to inhibit mast cell degranulation. For example, the method can be used to treat inflammatory responses associated with disorders such inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis) (see col., 13, lines 34-45 in particular). The `501 patent teaches that agents described herein can be anything which binds to or interacts with CD81 and induces (i.e., activates) or enhances CD81-mediated signal transduction. For example, the agent can be a polyclonal or monoclonal antibody, such as an anti-CD81 antibody. In particular embodiments, the antibody is 5D1 or 1A12 (see col., 9, line 65 to col., 10, line 3 in particular). The `501 patent further teaches that injections of anti-CD81 yielded significant inhibition of PCA reactions (blocks a biological activity of CD81) (see FIG. 10B). The functional properties claimed in claim 32 are inherent.

While the `501 patent and `647 publication is silent with respect to mast cell degranulation is involved with in the pathogenesis of IBD, however, inhibiting mast cell degranulation is involved in the pathogenesis of IBD as evidenced by He SH article. He article discusses the connections between current anti-IBD therapies or potential therapies for IBD with mast cells, implicating further that mast cell is a key cell type that is involved in the pathogenesis of IBD (see abstract). He article teaches that mast cell degranulation is involved in the pathogenesis of IBD (see abstract). He article teaches that mast cell tryptase inhibitor APC2059 was effective and safe in treating ulcerative colitis. The beneficial effects of 5-aminosalicylic acid on IBD were at least partially due to its mast cell stabilizing activity. Similarly, the effective treatment of IBD by corticosteroids might also be partially associated with its action on mast cells as significantly reduced numbers of mast cells were observed in the colon throughout steroid

therapy. He article teaches that ketotifen, a mast cell stabilizer, was able to significantly decrease mucosal damage of ulcerative colitis in an experimental colitis model and inhibit accumulation of PGE2, ITB4 and LTC4 in ulcerative colitis colon mucosa organ-culture, suggesting that this antiasthma drug may be useful for the treatment of IBD. Indeed, ketotifen was revealed to be effective in treating IBD with 5-aminosalicylate intolerance, and acute ulcerative colitis in children, most likely through inhibition of mast cell and neutrophil degranulation. It was surprising to learn that even immunomodulatory drug methotrexate, which showed promise in Crohn's disease therapy was able to inhibit heparin synthesis in mast cells, suggesting that the beneficial action of methotrexate on Crohn's disease might be due to the reduction of heparin secretion from mast cells. The association of these therapies with mast cells strongly indicates that mast cells are key cells in the development of IBD (see page 313-314 under RELATIONSHIP BETWEEN THERAPIES FOR IBD AND MAST CELLS).

The reference differs from the claimed invention in that the specific process as claimed is not expressly exemplifying a patient.

However, the method, in the `501 patent, is disclosed as being suitable to treat any inflammatory condition, which, of course, includes inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis) (see col., 13, lines 34-45 in particular). Clearly the disclosure of the reference also encompasses "improving" inflammatory bowel disease. In addition, the `501 patent teaches that agents described herein can be any molecule which binds to or interacts with CD81 and induces (i.e., activates) or enhances CD81-mediated signal transduction. The reference specifically teaches that the agent can be a polyclonal or monoclonal antibody, such as an anti-CD81 antibody. In particular embodiments, the antibody is 5D1 or 1A12 (see col., 9, line 65 to col., 10, line 3 in particular). The `501 patent uses 50 μg/275-300g (i.e., 0.17-0.18 mg/kg) of anti-CD81 antibodies (see col., 18, lines 10-15).

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success of improving or treating inflammatory bowel disease according to the teachings of '501 by providing an anti-CD-81 antibody to a patient suffering from this disease inasmuch as the reference discloses that such agents are suitable to treat inflammatory responses associated with disorders such as inflammatory bowel disease and it discloses two specific examples of such anti-CD-81 antibodies.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process taught by '501 by providing an anti-CD-81 antibody to a patient suffering from inflammatory bowel disease patient by providing specific anti-CD-81 antibodies to such a patient for the expected benefit of improving or treating the painful and distressing condition of inflammatory bowel disease. It would be conventional and within the skill of the art to easily adapt the teachings of the `501 patent to treat inflammatory bowel disease patients with an anti-CD-81 antibody.

Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to deduce from the reference teaching that the method of treating inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis) works in patients.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments in conjunction with *In re Vaeck*, 03/16/2011, have been fully considered but are not found convincing.

Applicants submit that, even assuming *arguendo* that Fleming et al. or Curd et al. suggests, amongst a plethora of other treatment methods, the possibility of treating inflammatory bowel disease by administering an anti-CD81 antibody, those of ordinary skill in the art at the time of the invention would not have possessed a reasonable expectation of success in treating inflammatory bowel disease with an anti-CD81 antibody. Applicants submit that this is, in part, because they would have recognized not only a predominant role for pro- inflammatory cytokines, such as TNF-α, in the pathogenesis of inflammatory bowel disease, but they would also have recognized the pivotal role of T-lymphocyte activation in the production of such pro-inflammatory cytokines in the bowel mucosa. Applicants point to Neurath et al. (Eur. J. Immunol, 1997, 27:1743-1750), authored by Markus Neurath, an internationally-recognized authority on inflammatory bowel disease research, discloses that TNF-α has a predominant pathogenic role in colitis in mice. For example, Neurath et al. experimentally demonstrates that macrophages in the lamina propria produced high levels of TNF-Gt in inflammatory bowel disease, and notes that the majority of recent colitis models have revealed that the inflammation is mediated by CD4+ T-lymphocytes producing high amounts of IFN-7 and TNF-α.

Further, Von Montfrans et al. (Mediators of Inflammation, 1998, 7:149-152)9 discloses that, following analysis of numerous studies on a variety of different inflammatory bowel disease animal models, the collective conclusion is that an overactive "antigen-dependent(CD4+) T lymphocyte activation will result in a high production of pro-inflammatory cytokines within the mucosal compartment and [result] in inflammatory bowel disease." Accordingly, Montfrans et al. and Neurath et al., published prior to the time of the invention (and which form part of the state of the art at the time of the invention), demonstrate the predominant role for an overactive proinflammatory T-cell response, and the resulting overproduction of TNF-α by T-lymphocytes and macrophages, in inflammatory bowel disease. These animal studies confirmed previous observations in humans, in which hyperresponsive T-lymphocytes localizing to the lamina propria in patients with inflammatory bowel disease were posited to contribute to local inflammation.

In contrast, however, Fleming et al. posits that inhibition of CD81 may inhibit mast cell degranulation, and lists inflammatory bowel disease, in amongst a plethora of other diseases, as a

disease that may potentially be treated by inhibiting CD81 (to inhibit mast cell degranulation). However, as shown by the above evidence - reflective of the knowledge of those of ordinary skill in the art at the time of the invention - it was understood that TNF-α production by T-lymphocytes and macrophages mediated the predominant inflammatory response in inflammatory bowel disease. For this reason, those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by targeting CD81 on mast cells - because they would have appreciated that such a method would not have targeted the predominant inflammatory response.

However, it appears that applicant arguing that inhibition of mast cell degranulation is not involved in IBD. Applicant appears to rely upon evidence that only TNF-α production by T-lymphocytes and macrophages mediated the predominant inflammatory response in inflammatory bowel disease. However, a person of ordinary skill in the art would have expectation of successfully using anti-CD81 antibodies, as is evidenced by He (World J Gastroenterol 2004;10(3):309-318). In contrast to applicant's evidence that those skilled in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease with anti-CD81 antibodies; He SH (World J Gastroenterol 2004;10(3):309-318) discloses role of mast cells and their major secretory products in inflammatory bowel disease. He article discusses the connections between current anti-IBD therapies or potential therapies for IBD with mast cells, implicating further that mast cell is a key cell type that is involved in the pathogenesis of IBD (see abstract). He article teaches that mast cell degranulation is involved in the pathogenesis of IBD (see abstract). He article teaches that mast cell tryptase inhibitor APC2059 was effective and safe in treating ulcerative colitis. The beneficial effects of 5-aminosalicylic acid on IBD were at least partially due to its mast cell stabilizing activity. Similarly, the effective treatment of IBD by corticosteroids might also be partially associated with its action on mast cells as significantly reduced numbers of mast cells were observed in the colon throughout steroid therapy. He article teaches that ketotifen, a mast cell stabilizer, was able to significantly decrease mucosal damage of ulcerative colitis in an experimental colitis model and inhibit accumulation of PGE2, ITB4 and LTC4 in ulcerative colitis colon mucosa organ-culture, suggesting that this antiasthma drug may be useful for the treatment of IBD. Indeed, ketotifen was revealed to be effective in treating IBD with 5-aminosalicylate intolerance, and acute ulcerative colitis in children, most likely through inhibition of mast cell and neutrophil degranulation. It was surprising to learn that even immunomodulatory drug methotrexate, which showed promise in Crohn's disease therapy was able to inhibit heparin synthesis in mast cells, suggesting that the beneficial action of methotrexate on Crohn's disease might be due to the reduction of heparin secretion from mast cells. The association of these therapies with mast cells strongly indicates that mast cells are key cells in the development of IBD (see page 313-314 under RELATIONSHIP BETWEEN THERAPIES FOR IBD AND MAST CELLS).

9. Claims 19, 20 and 31-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US. Patent 6,423,501 OR WO 98/25647 OR 7,026,283, each in view of Stoyanova et al (acta histochem. 104(2) 185–192 (2002).

The teachings of `501 patent, the `647 publication have been discussed, supra.

The `283 patent teaches and claims a method of treating an allergic or inflammatory condition associated with FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation comprising administering to a mammal an effective amount of an antibody that binds to CD81 and inhibits FcεRI-mediated degranulation and/or FcγRIII-mediated degranulation (see patented claim 1), wherein the antibody that binds to CD81 is a monoclonal antibody (see patented claim 3) or a polyclonal antibody (see patented claim 10), wherein the allergic or inflammatory condition associated with FcεRI -mediated degranulation and/or FcγRIII-mediated degranulation is an allergic or inflammatory condition associated with FcγRIII-mediated degranulation (see patented claim 7), wherein the allergic or inflammatory condition associated with FcεRI -mediated degranulation and/or FcγRIII-mediated degranulation is an allergic or inflammatory condition associated with FcγRIII-mediated degranulation (see patented claim 8), wherein the allergic or inflammatory condition is characterized by mast cell activation (see patented claim 15).
The `283 patent further teaches that the inflammatory condition associated inflammatory bowel disease (i.e., Crohn's disease and ulcerative colitis) (see col.,13 and 14, bridging ¶).

The claimed invention differed from the reference teachings only in the recitation the inflammatory condition is colitis (IBD).

However, Stoyanova et al chronic ulcerative colitis (CUC) is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders (see page 185, under Introduction). Stoyanova et al teach that the relationship of mast cells and inflammatory mediators in chronic ulcerative colitis. Stoyanova et al teach that mast cells play a significant role in the progress and maintenance of inflammatory processes in chronic ulcerative colitis (CUC) (see abstract). Stoyanova et al teach that mast cells are granular tissue cells with an established role in a variety of pathological processes including IBD (see page 186, 1st col., top ¶). Stoyanova et al teach that their study provides evidence for the important role of mast cells in the pathogenesis of IBD (see page 191, last ¶). Stoyanova et al teach that the number of these SP-positive mast cells and SER-positive mast cells were significantly increased in CUC as compared with controls (see table 1 and 3). At the ultrastructural level, some SER-positive mast cells were degranulating in the lumen of mucosal glands (Fig. 3). Further, the number of tryptase-positive mast cells was significantly increased in all colonic structures of patients with CUC in comparison with controls (Table 2). SP released from peripheral intrinsic or extrinsic sensory nerves can induce mast cells degranulation via a mechanism that is not receptor mediated. SP is attracted to membranes containing anionic lipids, and its carboxyl terminus is directed into the hydrophobic compartment of these membranes, directly activating G proteins to induce degranulation. This suggests that the effect of SP on mast cells may represent an adaptive response to environmental changes that is not mediated via synaptic junctions or membrane-bound receptors (see page 191, 1st col., tope ¶).

Those of skill in the art would have had reason to use the anti-CD81 antibody of the `501 patent, the `647 publication and `283 patent for the treatment CUC taught in `501 patent, the `647 publication, `283 patent and Stoyanova because anti-CD81 antibody would inhibit mast cells degranulation including inflammatory mediators in chronic ulcerative colitis.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 19-20 and 31-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/67796 to Curd et al for the same reasons set forth in the previous Office Actions.

Applicant's arguments in conjunction with *In re Vaeck*, 03/16/2011, have been fully considered but are not found convincing.

Applicant argues that Curd et al. posits that inhibition of CD81 on B-cells may be used for the treatment of autoimmune diseases. Curd et al. lists inflammatory bowel disease, in amongst a plethora of other diseases, as an autoimmune disease that may potentially be treated by inhibiting CD81. For the same reasons, however, those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by targeting CD81 on B-cells - because they would have appreciated that such a method would not have targeted the predominant inflammatory response.
In addition to the above, Applicants respectfully point out that those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by administering an anti-CD81 antibody because of the broad expression, and differential effects, of CD81 on other cell types. As stated by Witherden et al. (J. Immunol., 2000, 165:1902-1909),~ "CD81 ... is expressed on a wide variety of tissues and cell types, including both B and T cells as well as epithelial cells, and has the capacity to associate with other cell surface proteins in a cell type-specific manner." Thus, at the time of the invention, CD81 was known to be expressed on a wide variety of different cell types, and to interact with a variety of different cell surface proteins "in a cell type-specific manner."

In particular, Witherden et al. specifically discloses that CD81 was known at the time of the invention to be expressed, inter alia, on B-cells and T-cells. However, Witherden et al demonstrates that when CD81 on T-cells is targeted with antibody, it stimulates T-cell activation, resulting in enhanced production of proinflammatory cytokines, such as TNF-α and IFN-7. Therefore, because those of ordinary skill in the art at the time of the invention appreciated the predominant role of an overactive proinflammatory T-cell response - and the resulting TNF-α production by T-lymphocytes and macrophages - in causing inflammatory bowel disease (discussed above), they would not have possessed a reasonable expectation of success in treating

inflammatory bowel disease by administering an anti-CD81 antibody. This is because they would have recognized that, even when targeting CD81 on B-cells and mast cells, as posited by Curd et al. and Fleming et al., respectively, T-cells would also be targeted - resulting in enhanced production of proinflammatory cytokines such as TNF-α. Accordingly, due to the broad expression of CD81 on different cell types, and the cell type-specific functions of CD81 - in particular the stimulation of T-cells when cell-surface CD81 on T-cells is targeted by antibody - those of ordinary skill in the art would not have possessed any expectation that administering an anti-CD81 antibody would be effective in treating inflammatory bowel disease, much less possessed a reasonable expectation of success, as obviousness requires.
Applicants note that it is well-settled that in any obviousness inquiry, the person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. Certainly, at the time of the invention, Neurath et al. (and Montfrans et al., Emmrich et al. and Witherden et al.) would have been highly relevant to those of ordinary skill in the pertinent art contemplating targeting CD81 to treat inflammatory bowel disease. As such, the disclosures of Neurath et al., Montfrans et al., Emmrich et al. and Witherden et al. are highly relevant to this obviousness inquiry.

However, while Witherden et al teaches that when CD81 on T-cells is targeted with antibody, it stimulates T-cell activation, resulting in enhanced production of proinflammatory cytokines, such as TNF-α and IFN-γ, however, Curd et al teach that the use of antagonists such as antibody which binds CD81 (see published claims). Accordingly, Witherden et al supports the Examiner's position in that targeting CD81 on T-cells with antagonistic antibody would result in inhibiting production of proinflammatory cytokines, such as TNF-α and IFN-γ.

11. Claim 31 stands rejected under 35 U.S.C. 103(a) as being unpatentable over U.S Pat. No. 6,423,501 or WO 98/25647 as applied to claims 19-20 and 32 above and further in view of and Owens *et al* (1994) for the same reasons set forth in the previous Office Actions.

Applicant's arguments, filed 03/16/2011, have been fully considered, but have not been found convincing.

Applicants note that Owens et al. is directed to the production of variant antibody molecules, such as Fab, F(ab')2, Fv or scFv molecules. As such, Owens et al. does nothing to rectify the deficiencies of Fleming et al. and Curd et al., discussed above. Accordingly, those of ordinary skill in the art would not have arrived at the presently claimed invention for the same reasons as presented above, notwithstanding the disclosure of Owens et al.

It remains the Examiner's position that it is the Examiner's position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the anti–CD81 antibody taught by 6,423,501 or WO 98/25647 to Fab or F(ab')2 fragments taught by Owens et al. because the antibody fragments are the reagents of choice for

some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 22, 2011

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644